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ACADEMY OF DOCTORS
OF ACOLOGY®
The Role of Pharmaceutical Agents in Hearing Loss Management and Prevention

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Disclosure

• Dr. Campbell is the inventor on the patents for D-methionine as a protective agent.
• The patents are owned by her employer Southern Illinois University School of Medicine.
A Thank You

- National Institutes of Health
- US Department of Defense
- SIU School of Medicine
Otoprotective Agents

• Already in or approaching clinical trials for:
  • Protection from Cisplatin-Induced Ototoxicity
  • Protection from Noise Induced Hearing Loss: TTS and PTS
  • Clinical trials to prevent Aminoglycoside Induced Hearing Loss are being planned
Today’s Lecture

• Will focus on the current state of the art.
• In the not too distant future, ototoprotective agents are likely to be a part of clinical practice.
• Currently no drug is FDA approved to prevent or treat hearing loss or tinnitus
D-methionine (D-met)

- Provides virtually complete protection from cisplatin-induced ototoxicity, also reduces other side effects
- No anti-tumor interference in appropriate tumor model and dosing ratio
- Provides excellent protection against aminoglycoside-induced hearing loss
- Excellent protection from noise-induced hearing loss for pre- only, pre/peri- and even initial post exposure administration up to 7 hours
- Excellent protection from radiation-induced oral mucositis
Current Status of D-met Research

- Approved by FDA and funded by the US Department of Defense (DoD) for Phase 3 clinical trials to prevent noise induced hearing loss (NIHL) and tinnitus with D-met in US soldiers during weapons training.
- Phase 2 clinical trials manuscripts for cisplatin otoprotection and radiation induced oral mucositis are in preparation for publication.
- Working with GOG on clinical trial design to prevent cisplatin induced side effects including ototoxicity and possibly radiation induced oral mucositis.
- More bench work also needed. Currently DoD funded for further studies of NIHL protection and rescue.
- Currently seeking licensure partner.
Otoprotective Agents in or Approaching Clinical Trials to Prevent Cisplatin Induced Ototoxicity

- Sodium Thiosulfate (STS) (delayed)
- Amifostine
- Ebselen
- N-acetylcysteine (NAC)
- D-methionine (D-met)
D-methionine (D-met)

• Provides complete protection from CDDP ototoxicity
• No anti-tumor interference in appropriate tumor model and dosing ratio
• Provides excellent protection against aminoglycoside-induced hearing loss
• Excellent protection from noise-induced hearing loss for pre/peri- and even post exposure administration
Pre-clinical Trials with D-methionine For Cisplatin Otoprotection

Have previously presented that injected D-met prevents cisplatin induced outer hair cell loss and strial damage.

The following are some additional studies for clinical consideration.
Conclusions

• D-met can completely protect against CDDP-induced ABR threshold shift, OHC loss, and strial damage
• D-met partially protects against CDDP-induced weight loss
• D-met provides nephroprotection
• Patent cover for neuroprotection, GI protection and alopecia
Other findings

• D-met can be administered directly to the round window and still protect against systemic or topical cisplatin-induced ototoxicity
• D-met protects against carboplatin-induced ototoxicity
• D-met protects against aminoglycoside-induced ototoxicity
• Some patients receive all 3 drugs
• D-met also can protect against NIHL
What are the next steps towards clinical use?
D-met Tumor Model Studies

• In vitro tumor model studies may not be relevant to clinical model
• In vivo model for ovarian cancer did not show anti-tumor interference (UCI Irvine)
• In vivo model for lung cancer did not show anti-tumor interference (OHSU)
Tumor Models

• Human ovarian cancer (OVCAR) grown as a xenograft in athymic nude mice
• 10 animals per cell
• CDDP given at 7.5 and 15 mg/kg, D-met 150 mg/kg
• High dose CDDP without D-met inhibited tumor growth but shortened survival
• D-met increased survival with high dose CDDP with no antitumor interference
• D-met did not change survival or tumor inhibition for low dose CDDP
• D-met alone did not change tumor growth
D-methionine does not interfere with antitumor activity of Cisplatin in ovarian cancer xenograft tumor model
Effect of MRX-1024 (oral 300mg/kg) on cisplatin and irradiated (4*5 days = 20Gy) SCCVII mice tumors n=5

![Graph showing relative tumor volume over time for different groups: Control, Cis+Rad, Meth+Cis+Rad. The graph displays data points with error bars indicating variability.](image)
Round Window Microcatheter
Oral D-methionine (MRX-1024) Significantly Protects Against Cisplatin-Induced Hearing Loss: a Phase II Study in Humans

Kathleen C.M. Campbell, Ravi Nayar, Sudhir Borgonha, Larry Hughes, Alnawez Rehemtulla, Brian Ross, Prasad Sunkara
Southern Illinois University School of Medicine, Springfield, IL
St. John’s National Academy of Sciences, Bangalore, India
Molecular Therapeutics, Ann Arbor, Michigan
MRX 1024: An oral formulation of D-methionine (D-met)

- MRX 1024 (study drug formulation) is packaged at 200 mg D-met/ml. Each bottle contains 50 ml in a 60 ml bottle. The formulation is stable for over 1 year even up to 40 degrees C.

- The Placebo and MRX 1024 have the following excipients (GM/60 ML):
  - Methyl Paraben: 0.060
  - Propyl Paraben: 0.006
  - Xantan Gum: 0.072
  - Tween 80: 0.060
  - Sorbitol: 3gm
  - Orange Flavor: 0.1 ml
  - Purified water: up to 60 ml.
Study Design: Subjects

- Double blind randomized study
- 14 adults received 100mg/kg MRX 1024 1 hour prior to each dose of 50 mg/M2 cisplatin (Mean 263.57, SD 74.79)
- 13 adults received flavor matched placebo (Mean 253.85, SD 56.94)
- Primary tumor sites ranged from genitourinary tract to head and neck cancers
- Some patients also received radiation to the head and neck area but patients with radiation to the auditory pathway were excluded
Drug Administration

- Cisplatin was administered at the dose of 50mg/M2 body surface area. An antiemetic (Granisetron) was administered prior to Cisplatin infusion. An intravenous vein was cannulated and intravenous infusion of saline started. Cisplatin was administered along with the saline (a total of 1 Liter) over a period of approximately 1 hour, which was followed by the administration of a diuretic (optional).

- MRX-1024 was administered orally at the dose of 100mg/kg one hour prior to the cisplatin. Patients were comfortably seated and the bottle #, batch # and randomization charts were checked. The allocated container was dispensed to each subject and the volume measured in a calibrated dispensing cup. The subject consumed the entire quantity dispensed in the presence of the clinical coordinator. The dispensing container was filled with water which the subject then also ingested.
Audiologic Procedures:

- All testing conducted with GSI 61 audiometers with appropriate earphones (TDH 39 for 8 kHz and below, Sennheiser HDA 200 for 10 kHz and above)
- Double walled sound booth
- Baseline audiometry 8, 10, 11.2, 12.5 kHz replicability within 5 dB, tympanometry, word recognition
- Modified Hughson-Westlake procedures for threshold determination
- Testing performed by licensed audiologists
- Any changes replicated within 24 hours to confirm
Data Analysis

• Three factor analysis of variance (ANOVA) with one between subjects factor (group) and two within subjects factors (pre-post, and ear).
• The results of these analyses yielded several higher order interactions, especially with ear.
• To further understand the data a separate analysis was performed on each ear to allow for a clearer interpretation of the remaining interaction terms.
• Both paired and independent t-tests were performed to conduct specific comparisons of interest.
Right Ear Shift Averages

- Placebo
- Experimental

- 8 kHz: p = 0.220
- 10 kHz: p = 0.185
- 11.2 kHz: p = 0.960
- 12.5 kHz: p = 0.198
Left Ear Shift Averages

8 kHz
- Placebo
- Experimental

10 kHz
- Placebo
- Experimental

11.2 kHz
- Placebo
- Experimental

12.5 kHz
- Placebo
- Experimental

P = 0.026
P = 0.002
P = 0.112
No Difference Between groups for:

- SIDE EFFECTS MONITORED:
  - Weight loss
  - Digestive/Gastrointestinal
  - Blood/Bone Marrow
  - Constitutional (eg fever, fatigue, dizzyness)
  - Musculoskeletal system
  - Pulmonary
  - Dermatologic
  - Neurologic
  - Body as a whole
Anti-tumor interference

• No difference between groups in tumor response or survival during the course of the study.

• Long term survival data not available because subjects returned to their homes across India at the end of the study.
Conclusions:

• Oral D-methionine can protect against cisplatin induced hearing loss in humans
• Further large scale clinical trials studies are needed to confirm these findings in larger patient populations
Protection from Aminoglycoside Ototoxicity

Gentamicin: Sha and Schacht 2000
Amikacin: Klemens et al 2003
Kanamycin: Campbell et al 2011
D-met Protection from Kanamycin-Induced Ototoxicity

K. Campbell, M. Cooper, N. Khardori, D. Fox, S. Verhulst, K. Seymour, R. Meech
Southern Illinois University School of Medicine
Introduction

• Clinical use of the aminoglycoside kanamycin sulfate is limited because of potentially severe ototoxicity and nephrotoxicity

• If these side effects could be reduced, kanamycin could safely treat a variety of gram-negative bacterial infections that may be resistant to other therapies
Susceptible Microbes

- *Staphylococcus aureus*
- *Staphylococcus epidermis*
- *Neisseria gonorrhoeae*
- *Haemophilus influenzae*
- *Escherichia coli*
- *Enterobacter spp*
- *Shigella spp*
- *Salmonella spp*
- *Klebsiella pneumoniae*
- *Serratia spp*
- *Providencia spp*
- Many strains of Proteus
Susceptible Microbes

- *Staphylococcus aureus* (MRSA, most common cause of external otitis)
- *Staphylococcus epidermis* (external otitis)
- *Neisseria gonorrhoeae* (STD)
- *Haemophilus influenzae* (otitis media, epiglottitis)
- *Escherichia coli*
- *Enterobacter* spp (bloodstream infections)
- *Shigella* spp (diarrhea)
- *Salmonella* spp
- *Klebsiella pneumonia* (chronic otitis media, pneumonia)
- *Serratia* spp (systemic infections, pneumonia in cystic fibrosis patients)
- *Providencia* spp (urinary tract)
- Many strains of *Proteus* (dental, head and neck infections)
Materials and Methods

• Two groups of ten male pigmented guinea pigs weighing 200-250 g (Elm Hill Labs) were treated with 50 mg/kg/day sc of kanamycin sulfate for 23 days. One group received 240 mg/kg/day ip D-met fractionated into 2 doses, one 15 minutes prior to the kanamycin and another 7 hours later. The other group received equivalent placebo.

• ABRs were recorded before (baseline) and 2, 4, and 6 weeks after initiating treatments using center frequencies of 4, 8, 14, and 20 kHz

• Cochleae were removed at sacrifice (6 weeks) and OHC counts were performed using scanning electron microscopy (SEM)
Best D-met Protection from Kanamycin Induced Ototoxicity at 6 weeks (300 mg/kg)
D-met Protection from Aminoglycoside Induced Hearing Loss

• D-met provides significant protection against amikacin-induced; gentamicin-induced, tobramycin-induced, and kanamycin induced hearing loss.

• Target clinical trials populations: cystic fibrosis patients, and resistant strain TB patients
Other findings and future directions

• D-met can protect against amikacin-induced, tobramycin-induced, and gentamicin-induced hearing loss

• In vitro and in vivo studies show no antimicrobial interference.

• Target populations for clinical trials include cystic fibrosis patients in the US and resistant strain TB patients in developing countries
Noise-Induced Hearing Loss (NIHL)

- Sensorineural hearing loss
  - Manifesting first in the mid-high frequencies 3-8 kHz (4 kHz notch)
- 26 million Americans, age 20–69, may be affected (NIDCD, 2008)
- Temporary threshold shift (TTS) vs. permanent threshold shift (PTS)
  - TTS - Initial, reversible hearing loss
  - PTS - Irreversible hearing loss
- Mechanisms of NIHL
  - Involved structures:
    - Outer hair cells (OHC) – most vulnerable
    - Inner hair cells, auditory nerve, stria vascularis and supporting cells
  - Mechanical damage
    - Important factor in intense sound exposures
  - Oxidative stress
    - Generation of reactive oxygen and nitrogen species (ROS & RNS) may lead to apoptotic and necrotic death of OHC’s, leading to hearing loss
Dietary Supplements

• Several NIHL otoprotective agents are also micronutrients:
  • Mg: fish, almonds, spinach, shrimp, bran
  • D-met: cheese, yogurt
  • NAC: brussel sprouts
  • Resveratrol: red wine
  • Selenium: Brazil nuts, N. Dak and S.Dak grown foods, prime component of ebselen
  • Alcohol: 2-4 drinks per day
Antioxidant therapies Approaching or in Clinical Trials

- Ebselen (TTS trial)
- ACE Mg (TTS trial)
- D-Methionine (D-MET) (PTS trial)

- N-Acetylcysteine (NAC) no protection in clinical trials (no further trials planned)
- Agents have good safety profile and oral bioavailability
Ebselen
A Catalyst for Hearing Loss Treatment
Eric D. Lynch, PhD
Otoprotection across frequencies

Continuous 4 hr noise exposure
4-16 kHz noise at 113 dBSPL
4 mg/kg SPI-1005, ABR at 9 wks post noise, n=8 (3 & 14d), n=6 (7d), SEM shown
Cytocochleogram analysis
3 wks post noise
Dietary Micronutrients

• Beta-carotene, Vitamins C and E, Magnesium
  – Beta-carotene: scavenges singlet oxygen, prevents lipid peroxidation
  – Vitamin E: reduces peroxyl radicals in lipid layer
  – Vitamin C: scavenges free radicals in aqueous phase
  – Magnesium: reduces noise-induced vasoconstriction, blocks NMDA receptors, prevents calcium influx and neural excitotoxicity

• Patent pending, University of Michigan
  – Inventors: Josef Miller, Colleen Le Prell, Jochen Schacht, Diane Prieskorn

• Option to license by OtoMedicine, Inc.
• Human trials beginning in 2008
Antioxidants plus magnesium reduce noise-induced hearing loss: additive effects

Threshold Shift (dB)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Saline</th>
<th>ACE</th>
<th>Mg</th>
<th>ACEMg</th>
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<tbody>
<tr>
<td>4 kHz</td>
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<tr>
<td>8 kHz</td>
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<tr>
<td>16 kHz</td>
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2.1 mg/kg beta-carotene, p.o., 71.4 mg/kg L-threoascorbic acid, s.c., 26 mg/kg trolox, s.c.; magnesium sulfate, 2.85 mmol/kg, equivalent to 343 mg/kg, s.c.; 1 hour pre and 5 days post.
Protection is greatest in the base of the cochlea

Hair Cell Loss (Percent)

Cochlear Position
(Distance from Apex, mm)

NaCl
Mg
ACE
ACEMg
Current Clinical Trials for Protection from TTS

- ACE Mg
- Ebselen
iPod® Study
University of Florida

• Three preliminary studies to confirm exposure that produces small, reversible TTS (10-12 subjects per study)
  – Paradigm developed for use assessing potential for otoprotective benefit of new therapies

• Rock or pop music delivered at 93, 98, or 100-dB (A) in-ear sound level for 4 hours using insert earphones

• Using OSHA criteria, after converting to FFE
  – 43% dose; 86 dose; 100% dose

• Dual IRB review at UF and UM; NIH DSMB oversight
Experimental Measures

• Pure-tone Audiometry
  – Conventional Frequencies (0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz)
  – Extended High Frequencies (10, 12.5, 14, and 16 kHz)
  – Pre, 15 min, 1 hr 15 min, 2 hr 15 min, and 3 hr 15 min post, 24 hours post; 1 week post
  – 2 dB step size, GSI 61 clinical audiometer
• Distortion Product Otoacoustic Emission (DPOAE) Input-Output Functions
  – f2=2, 3, 4, 6, 8, 12 kHz; f2/f1=1.2
  – L1=25-65 dB SPL in 5 dB steps, L1-L2=10 dB
  – DPOAE tests initiated after each audiometric test
• Tinnitus Surveys
  – Immediately post music and after each DPOAE test
Current Clinical Trials for Pharmacologic Otoprotection from PTS

- D-methionine (D-met)
D-methionine: putative mechanisms

• Unlike most amino acids, methionine is reversibly oxidized (Vogt 1995) and thus may serve as a free radical scavenger
• Methionine can provide cysteine, a precursor for glutathione (GSH) synthesis
• Can increase mitochondrial GSH levels and can prevent the efflux of GSH from injured cell
• May protect antioxidant enzyme levels
• D-met well tolerated even at high dosages
D-methionine: putative mechanisms (continued)

• At least for noise improves/protects GSH/GSSG ratio
• Preferable pharmacokinetics to L-met for protection
• Has been previously used in humans and animals
• Part of normal nutrition (particularly present in fermented proteins)
• Methionine part of protein and needed for protein formation
Kopke et al 2002

- Chinchilla model
- 105 dB SPL noise band centered at 4kHz
- D-met or ALCAR administered at 200mg/kg ip,
- Administered every 12 hours starting 48 hours prior to noise and 1 hour prior to the noise and then twice per day for 2 days following noise exposure
Met HC protection
D-met Post-Noise Rescue
Mitchell, Meech, Campbell

• D-met can be administered 1 hour after noise exposure and provide protection from permanent NIHL.
• Does not provide significant against TTS but only PTS.
• Methods: 6 hour: 105dB SPL 4kHz octave band noise, 200 mg/kg D-met 1 hour after exposure and 2 days BID.
• With 10 animals per group, significant protection at 2, 4, 6 & 8 kHz
D-met rescue from NIHL

D-Met Rescue From Noise-Induced Hearing Loss

ABR Threshold Shift From Baseline To 21 Days Post

- 2kHz
- 4kHz
- 6kHz
- 8kHz

Control
Treated

[Graph showing threshold shifts at different frequencies for baseline and post-treatment, with error bars and significance markers.]
D-Methionine as a Rescue Agent from Noise-Induced Hearing Loss: Observations of Efficacy at Different Administration Time Intervals Post-Noise Exposure

Campbell, Claussen, Meech, Verhulst, Fox, Hughes
Hearing Research 2011
D-methionine

- Optical isomer of essential amino acid L-methionine
- Otoprotectant
  - Protects from aminoglycoside and cisplatin induced hearing loss (Campbell et al., 2007)
  - Protects from NIHL when administered prior to, or 1 hour post-noise exposure (Campbell et al., 2007; Kopke et al., 2002)
- Antioxidative properties
  - Indirect: preserve one of cell’s intrinsic systems for mitigating oxidative stress (glutathione)
    - Provide substrate for glutathione (Lu, 1998)
    - Prevent cellular efflux of glutathione (Ghibelli et al., 1998)
  - Direct: reversibly oxidizable, serves as free radical scavenger (Vogt, 1995)
Personal Protective Equipment

NOISE

Ischemia/reperfusion

Mitochondrial activity

Glutamate excitotoxicity

PGF$_{2\alpha}$

↑ ROS & RNS
- superoxide
- hydroxyl radical
- hydrogen peroxide
- peroxynitrite

Leakage of cellular ROS & Fe$^{3+}$ [Fenton Reaction]

DNA & protein damage
- Lipid peroxidation (self perpetuating)

Apoptosis & necrosis (hair cell loss)

Hearing loss

Adapted from Henderson et al., 2006
Experimental Question

How long can D-methionine administration be delayed, post-noise exposure, and still provide protection from permanent noise-induced hearing loss?

Noise exposure may occur in unexpected situations, where the individual may not have access to personal protective equipment, creating the necessity for a “rescue agent”.

- Occupational exposure (firefighters, military, factory workers)
- Recreational exposure (concerts, fireworks, hunters, lawnmowers)
- Air bag deployment, alarm systems
Methods

• 3 y.o. male chinchilla laniger
  – Protocol approved by SIU-SOM Laboratory Animal Care & Use Committee
• 6hr 105 dB SPL octave band noise centered at 4kHz (sound booth in DLAM)
• D-methionine - 200mg/kg/dose i.p.
  – 4 dosing groups: starting 1, 3, 5 or 7 hours post-noise exposure + saline control started at 0 hours
  – Dosing continued for 2 days, twice a day (5 doses total)
Methods

• Electrophysiologic measures
  – Auditory brainstem response (ABR)
    • 2, 4, 6 & 8 kHz
    • 4 assessments: baseline + 24hr, 14 days and 21 days post-noise exposure
    • Auditory thresholds measured
      – 100 dB SPL → 0 dB SPL (10 dB SPL increments)
      – Threshold level = minimum intensity at which visually replicable response is observed
    • Threshold shift from baseline determined

• Histologic analysis (in process)
  – Cochleae removed after 21 day ABR assessment
  – 2, 4, 6 & 8 kHz regions observed under scanning electron microscopy
  – 3 rows of 11 OHC’s (33 total) per region are sampled
  – Quantification of OHC loss and observation of morphological changes
  – Method shown to correlate with cisplatin induced ototoxicity (Campbell et al., 1996)
Methods

• Analysis
  – Recent data + pilot data
  – Left and right ear ABR data of each chinchilla pooled as one sample
  – Factorial ANOVA
    • 1 between factor (rescue interval)
    • 2 within factors (test day, test frequency)
  – Post hoc testing:
    • Dunnett’s test, comparing experimental to control group
Rescue from NIHL at Various Time Delays

21 day post noise

Control 3 hour 5 hour 7 hour

- 2kHz
- 4kHz
- 6kHz
- 8kHz
D-Methionine (D-met)

- D-met was first discovered to protect against hearing loss caused from a chemotherapy drug (cisplatin) in 1996 by Dr. Kathleen Campbell at Southern Illinois University School of Medicine (Campbell, et al., 1996).

- Methionine is a micronutrient, (i.e. found in cheese and yogurt) and is not alien to the human system.

- Methionine comprises 26 mg/g high quality protein in the diet (National Academy of Sciences 1980).

- D-met has been studied in human clinical trials (India) for chemotherapy (cisplatin) induced hearing loss with no side effects greater in the D-met group than in the placebo group at the same dosing level proposed for this study (100 mg/kg/day).

- Methionine has been studied for decades as a part of human and animal nutrition.
D-met Protection from NIHL

• Protects from permanent threshold shift (PTS) in chinchillas when given 2 days before and after, noise exposure (Kopke 2002, Clifford et al 2011) and when given 1 hour before and after (Samson et al 2008)

• Protects from PTS when first started 1, 3, 5, or 7 hours after noise cessation (Campbell et al 2007, 2011)

• Protects from temporary threshold shift when given just 1 hour before noise (Cheng et al 2008)
Results

• Overall, there was a trend of reduced threshold shift in all groups at each of the three post-noise exposure ABR assessments, reaching statistical significance (p<0.05) at the following points:
  – 1 day follow-up:
    • 3 hour group - 8 kHz
    • 7 hour group - 2, 6 & 8 kHz
  – 14 day follow-up:
    • 1 hour group - 8 kHz
    • 3 hour group - 2, 6, & 8 kHz
    • 5 hour group - 2 & 8 kHz
    • 7 hour group - 2 kHz
  – 21 day follow-up:
    • 1, 3, & 5 hour groups - 2, 4, 6 & 8 kHz
    • 7 hour group - 2, 4 & 8 kHz
Conclusions

D-methionine provided statistically significant (p<0.05) protection from noise-induced permanent ABR threshold shifts when administered within 5 hours after the noise exposure. At the 7 hour dosing epoch, statistically significant protection was obtained at the 2, 4 & 8 kHz frequencies.

We hope that this and future studies will lead to clinical therapies to rescue patients from permanent noise-induced hearing loss, such as on the battlefield.
Kathleen C.M. Campbell, PhD, CCC-A
Professor and Director of Audiology Research
Southern Illinois University School of Medicine
Departments of Surgery and Pharmacology
Springfield, Illinois

D-METHIONINE (D-MET) CLINICAL TRIALS FOR NOISE-INDUCED HEARING LOSS
Study Funding and Approvals

- Funded by the Department of Defense, U. S. Army Research and Materiel Command
- Reviewed and authorized to begin by the FDA
Previous D-met Clinical Trials (Phases 1-2)

- **Study #1:** Phase 1a: Pharmacokinetic Evaluation of D-met included 12 normal human adult volunteers.
- **Study #2:** Phase 1b: Open-label, multiple-dose, phase 1 study of D-met concurrent with radiation therapy with or without cisplatin. Purpose of the study was to evaluate the effect of D-met on radiation-induced oral mucositis in head and neck cancer. This study included 25 adult subjects with head and neck cancer (15 male/10 female; mean age 47 years).
- **Study #3:** Phase 2: Multi-center, randomized, double-blind, placebo-controlled, phase 2 study to evaluate the safety and effectiveness of D-met for mucosal protection in head and neck cancer patients. This study included 58 adult subjects (44 male/14 female; mean age 49 years).
- **Study #4:** Phase 2: Randomized, double-blind, placebo-controlled, phase 2 study to evaluate D-met protection in cisplatin-induced hearing loss. This study included 27 adult subjects (6 male/21 female; mean age 55 years).
Investigational New Drug Application (IND)

- IND application has been filed.
- We are approved to proceed and are collecting data.
- Application included drug formulation and testing, 2 species toxicology studies, 3 species PK studies, our published Phase I, all previous published animal and human data, all of our unpublished data, copies of all manuscripts (6,429 pages single copy)
- We have been invited to submit for Special Protocol Review (SPA)
Human Drug Formulation

• KP Pharmaceutical Inc.
• GMP formulated oral suspension
• Orange flavored with matching placebo
• 200 mg/ml
• Will be provided to site in individual doses for each subject
Current Clinical Trial Study Design

- Randomized, double-blind, parallel, placebo-controlled study
- Pure-tone air-conduction thresholds at .5, 1, 2, 3, 4, 6, 8 kHz
- Bone conduction at thresholds exceeding 15 dB HL
- Testing for permanent threshold shift only
- Tinnitus questionnaires modified from Tinnitus Ototoxicity Monitoring Interview (TOMI), Tinnitus Loudness Index, Tinnitus Handicap Index (THI)
- Independent statistical analysis at Yale: Carrie Redlich, MD, Marty Slade statistician
Site Selection

• Major Jillyen Curry-Mathis (Army Audiologist) initiated contact
• We spent approximately 10 months reviewing noise exposures in the various weapons training at Ft. Jackson and selected the Drill Sergeant Instructor Training School (DSS) during weapons training (minimum 500 rounds M-16 weapon fire in under 2 weeks) Multiple meetings: Ft. Jackson and elsewhere
• Current FT Jackson audiologists members of the DoD Hearing Center for Excellence (HCE)
   CPT Rebecca Ludwig
   CPT Jenny Davis
Advantages of Military Site Clinical Trials

• Very disciplined and motivated study team
• The training situation offers a very regimented environment for better controls
• Easy to add on study protocol as all weapons training already standardized for the Soldiers
• Drug dispensing can be readily dispensed and monitored
Possible Challenges of Military Site Clinical Trials

Conducting studies within the US military presents unique challenges differing from private/academic facilities

- Multiple approvals needed for clinical protocol. Approvals must be vetted up the chain of command
- Civilian researchers (like us) unfamiliar with military hierarchy, procedures, language and general culture (we are learning)
- Requires multiple collaborators, credit will be needed for everyone
- Military sites/personnel may be unfamiliar with clinical trials research
- Deployments cause staff turnovers
Additional Challenges

• Cooperative Research and Development Agreement (CRADA)
• Transferring Funds and hiring personnel on base
• Subjects have very limited time
• Space for equipment, testing and drug storage can be an issue
• Institutional Review Board (IRB)
• Multiple Military Divisions under Different Commands Involved
• Multiple levels of scientific review needed before study commencement
• FDA and IRB can require more measures but grant funding is limited
Institutional Review Board (IRB)

• The IRB of record for the study should be the IRB governing the study site institution
• IRB may be a regional IRB and not local to the site
• Military IRB requires “Impact Studies” to be conducted on all federal divisions participating in the study
• Second tier review/approval needed conducted by CIRO (Clinical Investigation Regulatory Office)
Next step?

- Clinical trials to compare efficacy and side effects for cisplatin, carboplatin, aminoglycoside and noise otoprotection and for radiation induced oral mucositis
- More work on mechanisms
- Hopefully more than one agent will be FDA approved for all of these applications in the not too distant future.
Clinical Trials Center at SIUSOM

- Sandy Puczynski, PhD, Director
- Joe Milbrandt, PhD, Clinical Trials Monitor
- Jill Anderson, AuD, PhD, Clinical Trials Coordinator
- Preclinical studies: Robert Meech, MA, Daniel Fox, MA, Tim Hargrove, PhD
- Tech Transfer: Rob Patino, Esq, Kristy Owen
My Sincerest Appreciation To:

- COL Traci Crawford, Commander, Moncrief Army Community Hospital
- CSM Lamont Christian, Commandant, US Army Drill SGT Academy
- LTC William Bimson, Deputy Commander of Clinical Services, MACH, Principal Investigator
- MAJ Christopher Wilson, Chief, Preventive Medicine MACH, Site Research Monitor
- MAJ Alfred Nader, Chief, Pathology, MACH
- MAJ Tracy Morning, Chief, Pharmacy, MACH
- CPT Rebecca Ludwig, Chief, Fort Jackson Hearing Program, Supervising Audiologist, Sub-Investigator
- CPT Jenny Davis, Audiologist, Sub-Investigator
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Discussion and Questions